

### **REMARKS**

Claims 1-10 are pending and under consideration in the present application.

Applicants acknowledge and thank the Examiner for withdrawing all of the rejections that were raised in the previous Office Action dated September 8, 2008 (i.e., the rejection of claim 10 under 35 U.S.C. § 112, first paragraph, the rejection of claim 10 under 35 U.S.C. § 112, second paragraph, the anticipation rejection of claims 1-9 under 35 U.S.C. § 102(a) based upon Mironov et al., and the anticipation rejection of claims 1-10 under 35 U.S.C. § 103(a) based upon Mironov et al., in view of Vozzi et al.).

As an initial matter, Applicants do not understand the timing of the Examiner's newly raised rejections in the Office Action dated May 29, 2009, which are addressed herein below. As detailed directly above, all of the rejections raised in the most previous Office Action dated September 8, 2008 were overcome with argument (i.e., no claim amendments were submitted). Thus, the present Office Action citing new §101, §112, and § 102 rejections, as well as citing new art, is repugnant to the principles of compact prosecution set for in MPEP §2106.

#### **Claim Amendments**

Claim 2 has been amended to delete the phrase "or other operations." No new matter has been added by way of this amendment.

Claim 5 has been amended to refer to step (c) of claim 1, rather than to nonexistent step (d). Applicants respectfully submit that the reference to nonexistent step (d) was a typographical error, and that no new matter has been added by way of this amendment.

#### **Previously raised rejection of claim 10 under 35 USC § 112, first paragraph and 35 USC § 112, second paragraph**

In the previous Office Action dated September 8, 2008, the Examiner rejected claim 10 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Moreover, the Examiner also rejected claim 10 under 35 USC § 112, second paragraph, for allegedly being indefinite. Specifically, the Examiner asserted that the claim limitation "simultaneous" is ambiguous in that it may include deposition at "the exact same place at the same exact time," which the Examiner asserts "does not appear to be possible."

In the previous response, Applicants argued that the “word “simultaneous” is defined as “existing or occurring at the same time.” (see simultaneous. (2009). In *Merriam-Webster Online Dictionary*. Retrieved March 5, 2009, from [www.merriam-webster.com/dictionary/simultaneous](http://www.merriam-webster.com/dictionary/simultaneous). The word simultaneous is not used inconsistently with this definition in the specification. **Nothing in this definition, or in the use of the term simultaneous, addresses any spatial relationship, as Examiner has asserted it might.** The Examiner has not cited any reference or text to support the contention that the term simultaneous in any context says anything at all about any spatial relationship.” (emphasis added)

In the present Office Action, the Examiner has stated that he has withdrawn the previously raised rejection in view of the arguments and the definition provided by the Applicants, but has again improperly interpreted the term simultaneous to mean “simultaneously depositing **at different locations** at the same time.” The Examiner has not cited any reference or text to support his contention that the term simultaneous in any context says anything at all about any spatial relationship, yet he continues to press his improper interpretation nonetheless. Applicants again respectfully submit that the plain meaning of the term simultaneous is silent with regard to any spatial relationship. Applicants again further submit that the term simultaneous, as it is used in claim 10, is unambiguous and is used consistently with its plain meaning to describe a temporal relationship.

In light of the present arguments, Applicants respectfully request clarification from the Examiner regarding his improper interpretation of the term simultaneous, and absent clarification, Applicants request that the Examiner formally withdraw his comments regarding this term.

**Rejection of claim 2 under 35 U.S.C. § 112, second paragraph**

Specifically, the Examiner asserts that the use of the phrase “or other operations” renders the claim indefinite for failing to point out what is included or excluded by the claim language. Although not necessarily agreeing with the Examiner, but in a good faith effort to further prosecution of the present application, Applicants have amended claim 2 to delete the phrase “or other operations.”

In light of the present amendment, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 2 under 35 U.S.C. § 112, second paragraph.

**Rejection of claim 3 under 35 U.S.C. § 112, second paragraph**

Specifically, the Examiner asserts that claim 3 is indefinite for not setting forth any steps involved in the process. Applicants respectfully submit that claim 3 depends from claim 1. Claim 1 sets forth at least 3 steps involved in the process. "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." MPEP 608.01(i). Therefore, claim 3 sets forth all the steps in the process as set forth in claim 1. Applicants note that the Examiner has not rejected claim 1 for being indefinite.

In light of the present arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. § 112, second paragraph.

**Rejection of claim 3 under 35 U.S.C. § 101**

Specifically, the Examiner asserts that claim 3 fails to set forth any steps involved in the process. Applicants respectfully submit that claim 3 depends from claim 1. Claim 1 sets forth at least 3 steps involved in the process. "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." MPEP 608.01(i). Therefore, claim 3 sets forth all the steps in the process as set forth in claim 1. Applicants note that the Examiner has not rejected claim 1 under § 101.

In light of the present arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. § 101.

**Rejection of claim 5 under 35 U.S.C. § 112, second paragraph**

Specifically, the Examiner asserts that the claim 5 is indefinite as improperly referring to step (d) of claim 1, but that claim 1 has no step (d). Applicants have amended claim 5 to refer to step (c) of claim 1. Applicants respectfully submit that no new matter has been added by way this amendment.

In light of the present amendment, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 5 under 35 U.S.C. § 112, second paragraph.

**Rejection of claims 1-10 under 35 USC § 102(e)**

Claims 1-10 under are rejected under 35 USC § 102(e) as allegedly anticipated by Boland et al. (U.S. Pat. No. 7,051,654; hereinafter “Boland”). Applicants respectfully submit that Boland does not anticipate claims 1-10 of invention for the following reasons. 35 U.S.C. § 102(e) provides that an applicant shall be entitled to a patent unless “the invention was described in ... a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent ....” Boland does not satisfy this requirement.

In view of the enclosed Declaration of Inventor Wei Sun under 37 C.F.R. § 1.131, Boland does not anticipate claims 1-10. The present application, U.S. App. Ser. No. 10/540,968, is a national stage entry application of PCT/US04/15316, filed May 14, 2004, which claims priority from U.S. Provisional App. No. 60/520,272, filed November 14, 2003. Boland was filed on September 17, 2003, published on December 2, 2004, issued as a patent on May 5, 2006, and claims priority to U.S. Provisional App. No. 60/747,469 which was filed on May 30, 2003.

Boland is not a proper 35 U.S.C. § 102(e) reference because Applicants of the present application invented the apparatus, as well as the processes the apparatus performs, before Boland, as evidenced by Mironov (of record, as well as enclosed as Exhibit A), which was published online on February 22, 2003. Prior invention by Applicants of the present invention is evidenced by the enclosed Declaration, as well as by the presence of the pictures of the apparatus shown in Figure 2a of Mironov, which were provided by Applicants of the present application to Vladimir Mironov, the lead author of Mironov, before Mironov was published online on February 22, 2003. Moreover, the descriptions of the structure and function of the apparatus depicted in Figure 2a of Mironov et al. were provided by Applicants of the present application to Vladimir Mironov before Mironov et al. was published, as evidenced by the enclosed Declaration. Furthermore, attached to the enclosed Declaration as Exhibits B, C and D are computer-generated graphics of the apparatus depicted in Figure 2a of Mironov, which were created by Applicants of the present application on a date prior to the publication of Mironov. Even assuming, *arguendo*, that the filing date of U.S. Provisional App. No. 60/747,469 is available as the critical date of the ‘654 patent under § 102(e), that filing date occurs after

February 22, 2003 and thus the '654 patent cannot anticipate the claims of the present application under § 102(e).

Moreover, applicants do not understand the timing of the Examiner's newly raised 102(e) rejection. In the Office Action dated September 8, 2008, the § 102(a) rejection based on Mironov was overcome and withdrawn by the Examiner in light of the previously submitted Declaration which established a date of invention prior to February 22, 2003. Thus, the present Office Action citing new art that is dated later than February 22, 2003 is repugnant to the principles of compact prosecution set for in MPEP §2106.

In light of the present arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-10 under 35 U.S.C. § 102(e).

**Summary**

Applicants respectfully submit that the arguments set forth herein evidence that the pending claims are in full condition for allowance. Accordingly, favorable examination of the claims is respectfully requested at the earliest possible time.

Respectfully submitted,

**WEI SUN, *ET AL.***

Date:

*August 28, 2009*

  
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

|            |  |   |
|------------|--|---|
| In re:     | Patent Application of<br>Wei SUN, <i>et al.</i>  | : Group Art Unit: 1649<br>:<br>:                      |
| Appln. No: | 10/540,968   | : Examiner: Hugh M. Jones<br>:<br>:                   |
| Filed:     | September 26, 2005   | :<br>: Attorney Docket No.:<br>: 046528-5047 (415078) |
| For:       | METHODS AND APPARATUS<br>FOR COMPUTER-AIDED<br>TISSUE ENGINEERING FOR<br>MODELING, DESIGN AND FREEFORM<br>FABRICATION OF TISSUE<br>SCAFFOLDS, CONSTRUCTS,<br>AND DEVICES | :<br>:<br>:<br>:<br>:<br>:<br>:                       |

**Declaration of WEI SUN, Ph.D, Under 37 C.F.R. § 1.131**

1. I, Wei Sun, am a named co-inventor of the present application, U.S. App. Ser. No. 10/540,968.
2. I am a Professor of Mechanical Engineering and Biomedical Engineering at Drexel University.
3. The present application, U.S. App. Ser. No. 10/540,968, is a national stage entry application of PCT/US04/15316, filed May 14, 2004, which claims priority to U.S. Provisional App. No. 60/520,272, filed November 14, 2003.
4. This Declaration is offered as proof to establish that the subject matter of the presently claimed invention was invented by me prior to February 22, 2003.
5. Attached hereto as Exhibit A is a journal article authored by Mironov et al., which was available online on February 22, 2003.
6. I invented the claimed apparatus, as well as the claimed processes the apparatus performs, before Mironov et al. was published online on February 22, 2003, as evidenced by the presence of the pictures of the apparatus shown in Figure 2a of Mironov et al.
7. The picture shown in Figure 2a was provided by me to Vladimir Mironov, the lead author of Mironov et al., before Mironov et al. was published online on February 22, 2003.

8. The descriptions of the structure and function of the apparatus depicted in Figure 2a of Mironov et al. were provided by me to Vladimir Mironov before Mironov et al. was published.

9. Attached as Exhibits B, C and D are computer-generated graphics of the apparatus depicted in Figure 2a of Mironov et al. These computer-generated graphics were developed by me on a date prior to the publication of Mironov et al on February 22, 2003.

10. In the Office Action dated May 29, 2009, the Examiner cited U.S. Pat. No. 7,051,654 as a prior art reference under 35 U.S.C. § 102(e). U.S. Pat. No. 7,051,654 (hereinafter '654) was filed on September 17, 2003, published on December 2, 2004, issued as a patent on May 5, 2006, and claims priority to U.S. Provisional App. No. 60/747,469 which was filed on May 30, 2003.

11. Regardless of what the '654 patent allegedly discloses, I invented the claimed features of the presently claimed apparatus prior to February 22, 2003, as evidenced by the attached Exhibits A-D. February 22, 2003 is earlier than the critical date of the '654 patent under § 102(e). Even assuming, *arguendo*, that the filing date of U.S. Provisional App. No. 60/747,469 is available as the critical date of the '654 patent under § 102(e), that filing date occurs after February 22, 2003. Therefore, I invented the claimed features of the presently claimed apparatus prior to whatever is disclosed and described in the '654 patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

August 26, 2009

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(date)



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Wei Sun, Ph.D.





# Organ printing: computer-aided jet-based 3D tissue engineering

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Tissue engineering technology promises to solve the organ transplantation crisis. However, assembly of vascularized 3D soft organs remains a big challenge. Organ printing, which we define as computer-aided, jet-based 3D tissue-engineering of living human organs, offers a possible solution. Organ printing involves three sequential steps: pre-processing or development of 'blueprints' for organs; processing or actual organ printing; and postprocessing or organ conditioning and accelerated organ maturation. A cell printer that can print gels, single cells and cell aggregates has been developed. Layer-by-layer sequentially placed and solidified thin layers of a thermo-reversible gel could serve as 'printing paper'. Combination of an engineering approach with the developmental biology concept of embryonic tissue fluidity enables the creation of a new rapid prototyping 3D organ printing technology, which will dramatically accelerate and optimize tissue and organ assembly.

*'Give us the tools and we will finish the job'*

-Winston Churchill

Although the terms 'tissue engineering' and 'organ printing' were introduced only recently (1987 and 1999 respectively), the study of cell coalescence and tissue assembly has a much longer history and is deeply rooted in developmental biology [1]. The classic work of several generations of outstanding marine and developmental biologists studying cell and tissue coalescence phenomena [2,3], tissue affinity [4], cell adhesion [5] and especially the fluidity of embryonic tissues [6,7] built the biological foundation for modern tissue engineering. In recognition of this, special chapters on developmental biology are included in modern tissue-engineering textbooks [8]. Tissue engineering itself is now often considered to represent a type of applied developmental biology [9]. Organ printing – the application of the principles of rapid prototyping technology (i.e. layer by layer deposition of cells or matrix) – is evolving into a promising approach for engineering new tissues or organs. Here, we show how developmental biology can be applied to organ printing and describe the essential steps and elements of this

novel technology. We discuss the challenging technological barriers, the possible strategies to overcome them and estimate the overall feasibility of printing 3D human tissues and organs.

## *'Secundum Naturam or Contra Naturam?'*

The fact that tissues, such as a blood vessel, can be successfully assembled without any synthetic polymer [10,11] supports our strong opinion that future progress in the field of tissue engineering will be increasingly based and dependent on the effective application of principles of developmental biology. It is safe to predict that the credo of the next generation of tissue engineers will be '*secundum naturam*' (according to nature) not '*contra natura*' (against

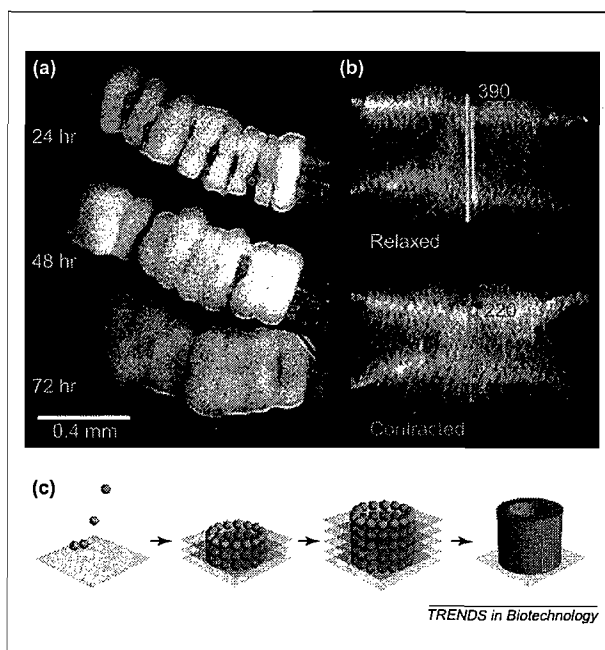


Fig. 1. Fusion of embryonic myocardial ring. Myocardium rings were cut from Stage 15–16 HH chick ventricle, containing only myocardium, endocardium and some intervening matrix. Isolated rings beat steadily for several days; (a) adjacent apposed rings fused overnight and (b) beat as one. (c). Schematic representation of principle of organ printing technology: placing of cell aggregates layer by layer in solidifying thermo-reversible gel with sequential cell aggregate fusion and morphing into 3D tube. This information is taken from [8].

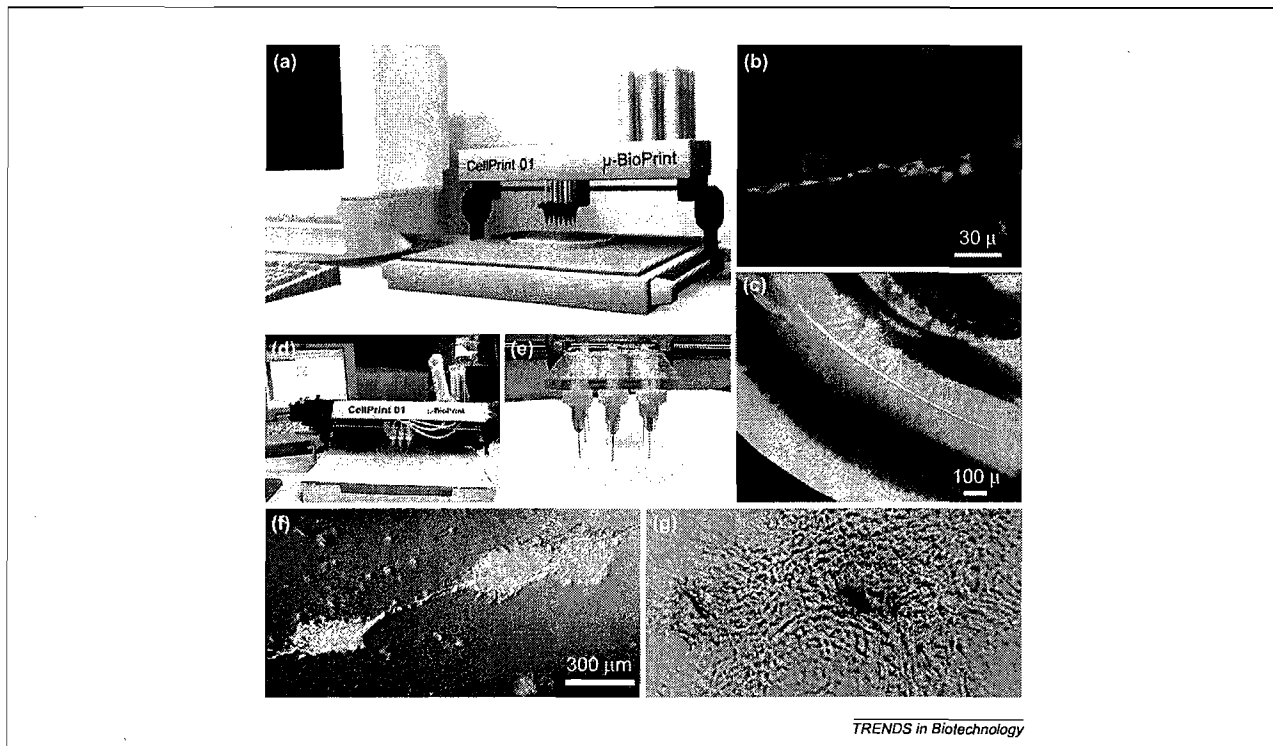
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nature). Both tissue engineering and developmental biology currently deal with the processes of tissue self-assembly, extracellular matrix deposition and accumulation, and stem cells. We believe that the fusion of these fields could, and will, lead to unprecedented achievements.

Another factor that we believe will accelerate the development of organ printing is time. Tissue engineers, as well as doctors and their patients, do not have the luxury to wait years until engineered tissues and organs become morphologically, biochemically, mechanically and functionally differentiated. Existing tissue technologies do not enable rapid assembling of tissues and organs. The timing issue can be addressed by developmental biology, in which we have learned that embryonic tissues are qualitatively and quantitatively viscoelastic fluids [6,7] with well described flow and fusion behavior. As the work by Thompson *et al.* [8] demonstrates, when embryonic avian heart tubes are initially cut into isolated myocardial 'rings' and placed on a supporting tubular framework in close apposition, they fuse and morph overnight into a single, synchronized, beating heart tube (Fig. 1a,b). The processes involved in this fusion process are still not completely understood, but the nature and time-scale of this phenomenon is inspiring for tissue engineers. Probable candidates for tissue fusion processes include remodeling of the extracellular matrix, cell migration,

re-establishment of cell-to-cell contacts or combinations of all these. However, the above simple developmental biological experiment provided us with a powerful insight, which represents a starting point to the proposed concept of organ printing as laid down in present work.

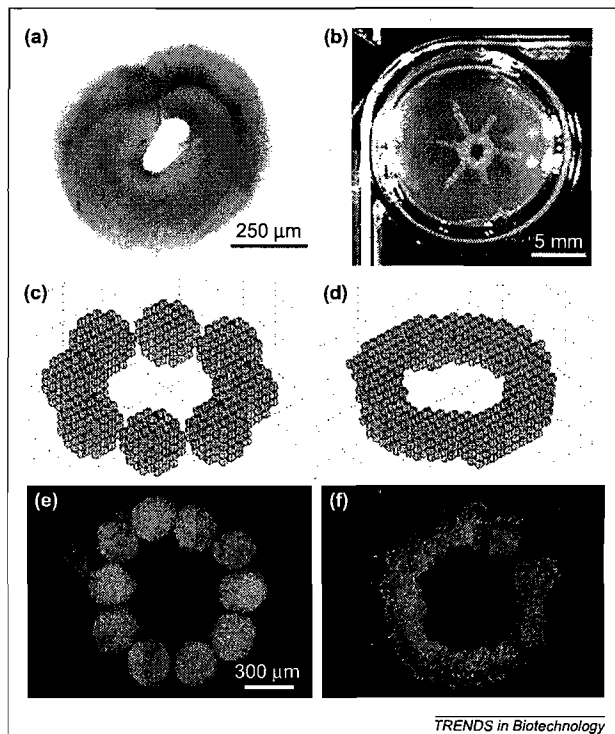
In analogy with the embryonic heart ring fusion experiment, we hypothesize that if cell aggregates are placed in close apposition within a 3D matrix, they fuse to form a complete disc or tube of tissue. Thus, the intrinsic capacity of closely placed soft tissue fragments or cell aggregates to fuse is the biological foundation on which organ printing technology will be developed (Fig. 1c). Recently, an explanation for the phenomenon of tissue fusion (considered a time-dependent process) has emerged. Using direct quantitative measurements, it was shown that embryonic tissues are viscoelastic fluids [6,7] and, as such, can flow and fuse. Organ printing attempts to apply microfluidic design to cells and cell aggregates triggering biologically relevant phenomena such as fusion. Interestingly, the potential of isolated tissue fragments to regenerate into tissues was originally demonstrated in 1907 by marine biologist Henry von Peters Wilson in his classic studies of coalescence phenomena in dissociated sponges [2] and further supported by Holtfreter [4]. However, it has taken many decades to recognize the technological potential and implications of this fundamental observation for tissue engineering.



**Fig. 2.** Cell printer and images of printed cells and tissue constructs. (a) Computer aided design-based presentation of model of cell printer. (b) Bovine aortic endothelial cells were printed in 50-micron size drops in a line. After 72 h the cells attached to the Matrigel support and maintained their respective positions. (c) Cross-section of the p(NIPA-co-DMAEA) gel showing the thickness of each sequentially placed layer. (d) Picture of the real cell printer and part of the print head with nine nozzles. (e) The printer is connected to a PtdCho via a bidirectional parallel cable together with 9 jets extent of mixing. We use HPGL2 format to send the printing information to the printer. Specifically, the printer nozzle selection (1-9), the X, Y, and Z coordinates to print a dot are transmitted to the printer, which is controlled by a Microchip PIC 16F877. Endothelial cell aggregates 'printed' on collagen before (f) and after their fusion (g). This information is taken from [18,21].

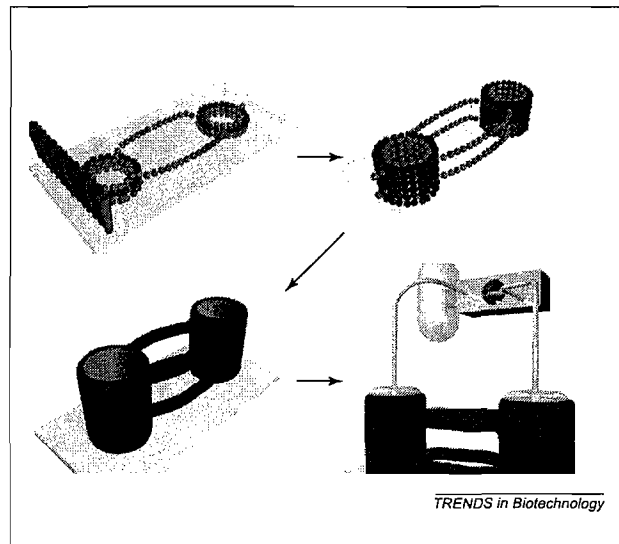
### What is organ printing?

Organ printing is a biomedically relevant variant of rapid prototyping technology, which is based on tissue fluidity. Computer-assisted deposition ('printing') of natural materials (cells or matrix) is done one layer at a time until a particular 3D form is achieved. However, recent attempts using rapid prototyping technologies to design solid synthetic scaffolds [12–15] suffer from the inability to precisely place cells or cell aggregates into a printed scaffold. Thus, we believe that organ-printing technology will become increasingly more '*secundum naturam*'. We define organ printing as a rapid prototyping computer-aided 3D printing technology, based on using layer by layer deposition of cell and/or cell aggregates into a 3D gel with sequential maturation of the printed construct into perfused and vascularized living tissue or organ (Figs 2–4). This definition of organ printing includes the many different printer designs and components of the deposition process such as, for example, jet-based cell printers, cell dispensers or bioplotters, the different types of 3D hydrogels and varying cell types.



**Fig. 3.** (a) Printed bagel-like ring that consists of several layers of sequentially (layer-by-layer) deposited collagen type 1 gel. (b) Manually printed living tube with radial branches from the chick 27stage HH embryonic heart cushion tissue placed in 3D collagen type 1 gel. Tube was formed as a result of fusion of three sequential rings. Every ring consists of 16–18 closed placed and fused embryonic cushion tissue explants. Image was taken after 24 h incubation in M199 medium with 10% of chicken serum plus ITS (insulin transferrin-selenium). (c,d) Mathematical model of cell aggregate behavior when implanted in a 3D model gel. (e) Eight aggregates each containing 123 cells before fusion. (f) Fused disc. (e,f) Fusion of aggregates of Chinese Hamster Ovary (CHO) cells implanted into RGD containing thermo-reversible gel and genetically labeled with green fluorescent protein. (e) Ten aggregates (containing ~5,000 cells) before fusion. (f) Final disc-like configuration after fusion. Note strong correlation between mathematical model and experimental data. This information is taken from [22].

<http://tibtec.trends.com>



**Fig. 4.** Printing, assembly and perfusion of an elementary printed 3D vascular unit; schematic representation. Endothelial cells aggregates are shown in red. Smooth muscle cells aggregates are shown in blue. After printing and fusion of cell aggregates the gel is removed from the lumen and large vessels are perfused with perfusion bioreactor.

The procedure of organ printing can be subdivided into three sequential steps: preprocessing, processing and postprocessing. Preprocessing primarily deals with the development of a computer-aided design (CAD) or blueprint of a specific organ. The design can be derived from digitized image reconstruction of a natural organ or tissue. Imaging data can be derived from various modalities including noninvasive scanning of the human body (e.g. MRI or computerized tomography) or a detailed 3D reconstruction of serial sections of specific organs (see [16] for a recent review).

Yet another approach to designing a tissue is based on mathematical modeling using a set of theoretical principles, rules or laws related to spatial organization. One the most impressive recent examples of this technology is called 'constrained constructed optimization' (CCO), which was developed by Karch *et al.* [17]. Processing usually refers to actual computer-aided printing or layer-by-layer placement of cells or cell aggregates into a 3D environment using CAD or blueprints. Finally, post-processing is concerned with the perfusion of printed organs and their biomechanical conditioning to both direct and accelerate organ maturation.

### Is organ printing a feasible technology?

To answer this question we define our goal as the successful reduction of complex tasks of organ tissue engineering into a series of simple, testable prototypes and pilot projects. Thus, our testing of the organ-printing hypothesis must include considerations based on results obtained from a series of crucial, well-designed, preliminary experiments. This minimal program must include: development of a printer which can print cells and/or aggregates; demonstration of a procedure for the 'layer by layer', sequential deposition and solidification of a thermo-reversible gel or

matrix and demonstration of fusion from closely placed cell aggregates into ring-like or tube-like structure within the gel. Achieving these goals will demonstrate the feasibility of our proposed definition for organ printing technology. To accomplish the first step, a new type of cell printer was developed [18], a device capable of printing single cells, cell aggregates and the supportive, biodegradable, thermo-sensitive gel according to a computer generated template (Figs 2,3a). Thermo-reversible gel [19–20] was printed one layer at a time, each on the other with individual layer thickness comparable to the diameter of the cell aggregates (Fig. 2) [21]. In accordance with mathematical predictions [22], it was shown that closely placed cell aggregates and embryonic heart mesenchymal (cushion tissue) fragments could fuse into ring and tube-like structures in 3D gel (Fig. 3). Thus, our pilot experiments strongly indicate the feasibility of organ printing technology.

### Why start from the printed tube?

In his seminal work, Danish Nobel Prize Laureate August Krogh [23] demonstrated that vascular density is the most crucial factor for adequate organ perfusion and supply of oxygen and functioning. More recently, Judah Folkman [24,25] introduced a global concept to explain angiogenic dependency of growth in both tumor and normal tissues. Without adequate vascularization, tissue-engineered organs could not survive and undergo intensive apoptosis and necrosis. Moreover, vascularization is often correctly identified as a main technological barrier for building 3D human organs [26–28]. The two main strategies proposed for inducing vascularization of tissue-engineered organs are either the incorporation of growth factors into the scaffold to induce angiogenesis after implantation or the pre-seeding of the implant with endothelial cells [27,28]. None of these strategies might prove satisfactory because of the slow rate of vascular tissue remodeling and the complex nature of the highly branched microvascular networks necessary for maintaining viable cell constructs. Sophisticated attempts to create 'room service-like' branching channels in solid scaffolds to improve the effectiveness of cell seeding fail to consider the key issue of the very nature of organ perfusion [28,29]. Effective organ perfusion is not possible without an endothelialized vascular tree. The proposed printing technology offers a unique opportunity to eventually print a complex branching vascular tree during the overall process of printing a complete organ. Such organs could be immediately perfused after printing (Fig. 4). The lumen of a printed tube could be opened and washed simply by changing the physical characteristics of the gel. Thus, the capacity to print a 3D tube not only is a logical initial step but also a very important indicator of the overall feasibility of proposed organ printing technology.

### Conclusion

Organ printing, or computer-aided layer-by-layer assembly of biological tissues and organs, is currently feasible, fast-evolving and predicted to be a major technology in tissue engineering. Organ printing uses the principle of cellular self-assembly into tissues [30] similar to the way embryonic-like tissues sort and fuse into functional forms dictated by

the rules laid out in developmental biology. Besides their obvious application for organ transplantation, 3D perfused, vascularized, printed human tissues (or structural-functional units of human organs) could become popular screening assays for drug discovery and testing and further biomedical research. It is safe to predict that in the 21st century, cell and organ printers will be as broadly used as biomedical research tools as was the electron microscope in the 20th century.

### Acknowledgements

We thank Robert Thompson, Chris Wilson, Elizabeth Roth, Anna Gutowska, Stephane Woerly, Adrian Neagu, Károly Jakab, Wei Sun, Vladimir Kasyanov and Sue Tjepkema-Burrows. This research was partly supported by NASA/EPSCOR grant 'Cardiovascular Tissue Engineering'. This research was partly supported by NASA/EPSCOR grant 'Cardiovascular Tissue Engineering' (to V.M. and R.M.) and NSF grant 'Biocomplexity' (to G.F.).

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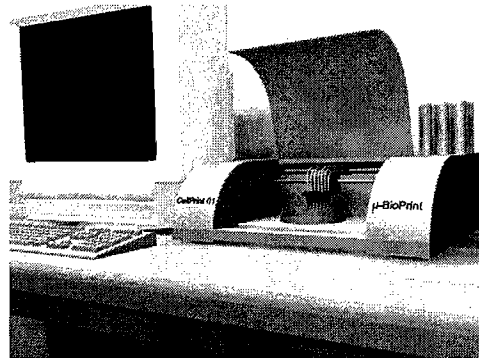
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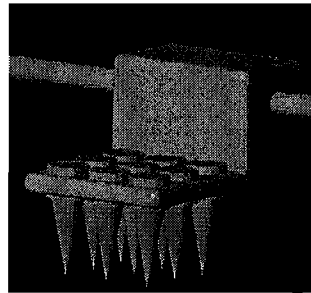
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**Exhibit B**



**Exhibit C**



**Exhibit D**

